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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/816,790	03/22/2001	Keith D. Allen	R-855	5557

26619 7590 10/23/2002

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EXAMINER
QIAN, CELINE X

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 10/23/2002

13

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/816,790	Applicant(s) ALLEN ET AL.	
	Examiner Celine X Qian	Art Unit 1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE ____ MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 July 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11-16 and 22-39* is/are pending in the application.

4a) Of the above claim(s) *11-16 and 22-25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claims 11-16 and 22-39 are pending in the application.

This Office Action is in response to the Amendment filed on 7/19/02.

Claims 11-16 and 22-25 are withdrawn from consideration for being directed to non-elected subject matter.

Response to Amendment

The rejection of claims 8 and 17-21 under 35 U.S.C. 112, first paragraph has been withdrawn in light of Applicants' cancellation of the claims.

The rejection of claims 1-4, 9, 10 and 17-21 under 35 U.S.C. 112, second paragraph has been withdrawn in light of Applicants' cancellation of the claims.

The rejection of claims 1-8 and 10 under 35 U.S.C. 103 (a) has been withdrawn in light of Applicants' cancellation of the claims.

The newly added claims 31-39 are rejected under 35 U.S.C. 112, first paragraph as discussed below.

The newly added claims 26-30 are rejected under 35 U.S.C. 103 (a) as discussed below.

New Grounds of Rejection Necessitated by Applicants' Amendment

Claim Rejections - 35 USC § 112

Claims 31-39 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a homozygous sulfotransferase knockout mouse lacks production of functional sulfotransferase protein, a method of making said mouse by introducing the knockout construct into embryonic stem (ES) cells, selecting ES cells comprising sulfotransferase

knockout construct, introducing said ES cells into blastocyst, and subsequently produce a transgenic knockout mouse, does not reasonably provide enablement for a transgenic mouse comprising any type of sulfotransferase protein, and a method of making said knockout mouse by introducing the knockout construct into any type of cell, or introducing ES cells directly into the pseudopregnant mouse. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The nature of the invention is a transgenic mouse comprising a disruption in a sulfotransferase gene and exhibits phenotype comprising aggressive, hyperactive, increased activity and decreased anxiety behavior; and a method of making said transgenic mouse. The specification discloses a method for generating said mouse by homologous recombination using a sulfotransferase construct (see page 55-60, examples 1-4). The specification further discloses that the homozygous knockout mice exhibit the phenotype comprising hyperactive and aggressive behavior (see page 60, lines 12-27).

When considering the predictability of this invention, one has to remember that many of the phenotypes examined in transgenic knockout models are influenced by the genetic background in which they are studied and the effect of allelic variation and the interaction between the allelic variants (pg.1425, col.1 1st paragraph, Sigmund, C.D. 2000. Arterioscler Thromb Vasc Biol.20:1425-1429). The specification discloses the phenotype of a homozygous sulfotransferase knockout mouse as exhibiting a behavioral abnormality. And the phenotype of said mouse is essential for the use of said transgenic knockout mouse.

The specification discloses that the word "disruption" comprises alter or replace a promoter, enhancer, or splice site of a target gene, and can alter the normal gene product by inhibiting its production partially or completely or by enhancing the normal product's activity (see page 9, lines 19-26). However, it is not known in the prior art that such "disruption," would produce the phenotype as disclosed by the specification. The specification only discloses a mouse with two alleles of sulfotransferase disrupted by inserting a selection marker that exhibits the phenotype comprising aggressive, hyperactive behavior. Thus, the phenotype of a transgenic mouse comprising any "disruption," as defined by the specification, in a sulfotransferase is unpredictable. Thus, the specification, in the instant case, is not enabling for transgenic knockout animals that exhibit no phenotype or that exhibit transgene-dependent phenotypes other than that disclosed in the instant specification. One skilled in the art would have to engage in undue amount of experimentation to make and use the invention commensurate in scope with these claims.

The specification teaches a method of making the sulfotransferase knockout mouse by introducing the knockout construct into embryonic stem (ES) cells, selecting ES cells comprising sulfotransferase knockout construct, introducing said ES cells into blastocyst, introducing the blastocyst into a pseudopregnant mouse, and subsequently generates a transgenic knockout mouse. However, the specification does not support a method of making said mouse by introducing the knockout construct into any type of cells (claim 36). In addition, the specification does not support such method as to introducing ES cells directly into a pseudopregnant mouse (claim 31). The prior art does not teach such methods either. Therefore,

one skilled in the art would have to engage in undue amount of experimentation to make and use the invention commensurate in scope with these claims.

This rejection may be overcome by amending the claims to recite only the transgenic knockout mouse that lacks production of functional sulfotransferase and exhibits the disclosed phenotype, recite ES cells in claim 36, and provide additional method steps in claim 31.

Claim Rejections - 35 USC § 103

Claims 26-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mansour et al (1988, Nature, vol. 336, No. 24, 348-352), in view of Kong et al. (1993, Biochimica et Biophysica Acta, vol. 1171, 315-318).

The claims are drawn to a sulfotransferase gene-targeting construct and a method of making said construct. The recitation of "wherein the targeting construct...exhibits a behavior abnormality" defines the intended use of the targeting construct, which does not carry patentable weight.

Mansour et al. teach a strategy for targeted disruption of the hprt and proto-oncogene int-2 in mice embryonic stem cells and subsequent generation of knockout mice. Their teaching addresses the previous technical difficulty of obtaining embryonic stem cell carrying non-selectable, targeted gene mutation at loci of interest, and therefore provides a model which can be used to produce homozygous mutation of any gene, regardless of its function, if a cloned fragment of the gene is available (see page 348, second paragraph, line 1-3, third paragraph, line 1-5, and page 352, fourth paragraph, line 1-3). Mansour et al. further teach the generation of two targeting constructs, pRV9.1/TK and pINT-2-N/TK, each contains two sequences from hprt and

int-2 respectively, and a neo selection marker in between the two sequences (see page 350, figure 3).

However, Mansour et al. do not teach how to make a sulfotransferase gene target construct and knockout mouse.

Kong et al. teach the cloning of a mouse sulfotransferase gene, mST, from mouse liver. They provide the cloned coding sequence for sulfotransferase gene (see page 316, figure 1). Kong et al. also teach that the sulfotransferase has been implicated in the activation of mutagens and carcinogens (see page 318, 1st col., 2nd paragraph, lines 1-6).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make a sulfotransferase knockout mouse to study the sulfontransferase function because its implication in activation of mutagens and carcinogens.

The ordinary artisan would have been motivated to knockout the function of sulfotransferase gene in a mouse to study the role this gene plays in the activation of mutagens and carcinogens in mouse (see page 318, 1st col., 2nd paragraph, lines 1-6).

The ordinary artisan would have had reasonable expectation of success because of the teachings of Mansour et al., who teach a general method of targeted gene disruption in mice based on homologous recombination using a cloned fragment of a desired gene, and Kong et al., who teach the coding sequence of the mouse sulfotransferase gene, and also teach the importance of this gene in activation of mutagens and carcinogens. Therefore, the invention would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

This application contains claims 11-16 and 22-25 drawn to an invention nonelected with traverse in Paper No. 9. A complete reply to the final rejection must include cancelation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celine X Qian whose telephone number is 703-306-0283. The examiner can normally be reached on 9:00-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Remy Yucel can be reached on 703-305-1998. The fax phone numbers for the

organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Celine Qian, Ph.D.
October 21, 2002

TERRY MCKELVEY
PRIMARY EXAMINER